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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/799,376	03/12/2004	Nina Finkelstein	1662/62005	7297

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EXAMINER	
MORRIS, PATRICIA L	
ART UNIT	PAPER NUMBER
1625	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/799,376	FINKELSTEIN ET AL.	
	Examiner	Art Unit	
	Patricia L. Morris	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *6-22,24-43 and 45-50* is/are pending in the application.

4a) Of the above claim(s) *6-12,19-22,24-40 and 45-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-18,41-43 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/14/08;4/4/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 13-18, 41-43 and 45 are under consideration in this application.

Claims 6-12, 19-22, 24-40 and 46-50 remain held withdrawn from consideration as being drawn to nonelected subject matter 37 CFR 1.142(b).

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 14, 2008 has been entered.

Election/Restrictions

The restriction requirement is deemed sound and proper and is hereby made maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 13-18, 41-43 and 45 are rejected under 35 U.S.C. 102(a), (b) and/or (e) as being anticipated by Avrutov et al., Maimo and Kohl et al. I, II for the reasons set forth in the previous Office action.

Again, Avrutov et al., Maimo and Kohl et al. I, II specifically disclose the instant compound. Note claim 22 of Kohl et al. I, example 4 of Arrutov et al. or example 18 of Maimo. Hence, the instant compound is deemed anticipated therefrom.

Contra to applicants' arguments in the instant response, a novel chemical product is identified first by its "chemical nature", i.e., elemental and atom content. It is a well known fact that many pharmaceutical solids exhibit polymorphism which is frequently defined as the ability of a substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice (see US Pharmacopia). Polymorphs are different crystalline forms of the **same pure substance** in which the molecules have different arrangements and/or different conformations of the molecules. Brittain concluded this per ponderous of conventional nature in the text book "Polymorphism in Pharmaceutical Solids" on page 2 that "*in the strictest sense, polymorphs are different crystalline forms of the* **same pure substance** *in which the molecules have different arrangements and/or different conformations of the molecules".*

The prior art pharmaceutical compositions and comprising the crystalline forms would be the same as the instant compositions comprising the crystalline forms, since the crystalline forms would no longer exist in solution, or after granulation, compaction or tableting process, as it is well known in the art that such process(es) would lead to alteration of the crystal structure. Note, for example, Chemical & Engineering News, pages 33-34. It is well known in the art that the

forms would lose their unique crystalline structure especially in solutions. The different arrangements and/or different conformations of the molecules disappear and are lost upon dissolution of the crystalline form in the body's aqueous environment. Rowland & Tozer illustrate the process by which pharmaceutical compositions travel through the body. See page 123. This graphic shows that the drug travels into the stomach, through the gut wall, into the portal vein to the liver. The drug that withstands the liver travels through the blood to a target site where it exhibits its therapeutic function. At the target sit, because the drug molecules bind to a receptor or enzyme one at a time, the crystal must be dissolved in order to bind. Silverman on page 73 pictorially illustrates molecular action of protein/substrate binding. Moreover, Jain et al. on page 316 recites that "polymorphs will be different in crystal structure but identical in the liquid or vapour states. Further, in the aqueous phase, all physical forms are amorphous (see Ulicky).

Claim Rejections - 35 USC э 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 13-18, 41-43 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Avrutov et al., Maimo and Kohl et al. I, II in view of Loqvist et al. (US 6,384,059), Finkelstein et al., Haleblian et al, Muzaffar et al., Chemical & Engineering News, US Pharmacopia., Jain et al, Taday et al., Brittain et al. and Concise Encyclopedia Chemistry for the reasons set forth in the previous Office action.

Again, Avrutov et al., Maimo and Kohl et al. I, II teach the crystal forms of the instant known compound and as well as the pharmaceutical compositions. Note example 4 of Avrutov et al. or claim 22 of Kohl. Loqvist et al. and Finkelstein et al. specifically teach that the instant compounds and analogous omeprazole are known to exist in additional crystalline forms. Haleblian et al., Muzaffar et al., Jain et al., Brittain et al. and Taday et al. teach that compounds exist as polymorphs. Chemical & Engineering News, Muzaffar et al., US Pharmacopia and Concise Encyclopedia teach that at any particular temperature and pressure, only one crystalline form is thermodynamically stable. Hence the claimed crystalline form as well as its relative selectivity of properties *vis-a-vis* the known compound are suggested by the references. It would appear obvious to one skilled in the art in view of the references that the instant compound would exist in different polymorphic forms. No unexpected or unobvious properties are noted.

One having ordinary skill in the art would find the claims prima facie obvious because the instant claims differ from the known product merely by forms and the physical properties innate to the forms. As it was recognized in the art that in the pharmaceutical field, many solids

exhibit polymorphism which is the innate nature of the particular drug (see US Pharmacopia #23, national formulary #18). There is nothing unobvious about the innate nature of a drug. It is also recognized in the art that the innately existing different "morph" will display different physical properties such as X-ray diffraction pattern, melting point etc. (see Brittain p. 178-179, 219). Just because it is "different" does not merit the new form patentability. As it was clearly stated by one having ordinary skill in the art in Brittain (p. 1-2) supra, as well as set forth by the court in In re Cofer 148 USPQ 268. Ex parte Hartop 139 USPQ 525, that products which are merely different forms of known compounds, notwithstanding that some desirable results are obtained therefrom, are unpatentable. The instant specification and claims disclosed known compound rabeprazole forms X and Y, which are the ***same pure substances*** as the prior art, only *have different arrangements and/or different conformations of the molecule*. Mere difference in physical property is well known conventional variation for the same pure substance (see Brittain p.1-2), i.e. prima facie obvious. For a known compound with defined chemical nature to be patentable for a new form, it must have a patentability basis of an advantage in terms of stability, formulation, solubility, bioavailability, easy of purification, preparation or synthesis, hygroscopicity, recovery or prevention of precipitation etc. (see Brittain p. 185). Even if the product of the instant application and the prior art differ in X-ray diffraction or "form", the mere difference in physical parameter such as X-ray diffraction pattern does not offer any unexpected advantage of prior art product with the same chemical property and biological property i.e. a mere variation in physical property which flows naturally with the changing form.

A state of the art reference from Wikipedia is added to rebut applicants' arguments to show further support that known compounds have polymorphic forms because "*every compound*

has different polymorphic forms, and that, in general, the number of forms known for a given compound is proportional to the time and money spent in research on that compound."

Claim Rejections - 35 USC ∋ 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 41-43 and 45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement as well as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention or was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is more nearly connected, to make and/or use the invention.

The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916), where the Supreme Court looked to whether the experimentation needed to practice an invention was undue or unreasonable. *Id.* An invention must be described so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). As stated in the MPEP 2164.01(a) "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". The analysis must consider all the evidence

related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole. *Id.* at 740, *Id.* at 1407. The factors to be considered herein are those set forth as the In re Wands, 8 USPQ 2nd 1400 (1988) decision.

> An analysis of enablement was made with the following evaluation:
> --a complete review of the state of the art with many references indicating the necessity of explicit and specific guidance for preparing pharmaceutical composition maintaining crystallinity of the active agent;
> --a complete review of the specification which only disclosed conventional carrier such as water, vegetable oil, alcohol (p.7) which are known to abolish crystallinity;
> --a complete review of the skill level of artisan in the field providing that the field is well aware of preserving crystallinity proper solid carrier, proper compression condition, etc. must provided for such composition to be available.

Nature of invention and breadth of the claims

Claims 41-43 are drawn to pharmaceutical composition comprising a compound keeping its crystalline property. The field of pharmaceutical composition of crystalline product is highly unpredictable and empirical. Further, claim 45 is drawn to a *method of inhibiting gastric acid in the stomach.*

It is well known in the art, at a given pressure and temperature only one thermodynamically stable crystalline form will exist for a given compound (see encyclopedia supra and US Pharmacopia). It is further well recognized in the art that when a crystalline form for a drug is prepared into a solid formulation, the "form" is expected to change in an unpredictable manner (Bakale et al. '646, col. 2, lines 32-34), eventually to the most thermodynamically stable one.

The state and skill level of the art and predictability

The state of the pharmaceutical composition containing polymorphic form art provided per ponderous of evidence that *unless specific and particular* conditions can be obtained, the formulation process would cause polymorphic forms to change. See :

--Muzaffar et al. p.60 "At any one temperature and pressure only one crystal form of a drug is stable and any other polymorph existing under these conditions will convert to the stable form .... " And p.63-65 (a)-(h) pharmaceutical preparing processes affect polymorphism;

--Jain et al. p.322-326, manufacturing processes that affect polymorphs ;

--Doelker et al. abstract "...a given drug, although chem. well defined, may exhibits quite different behavior. Process conditions (grinding, tableting, granulations, drying) may also affect secondary properties of the drug, such as compactibility, wetttability, soly, dissolution rate, bioavailability and even pharmacological, activity."

--Otsuka et al. p.852 ...in formulation studies and the method preparing CBZ has been shown to affect the drug's pharmaceutical properties through the polymorphic phase transformation of the bulk CBZ powder during the manufacturing process"

--Caira on page 165 states, "Manufacturing processes including crystallization scale-up, drying, heating, compression and milling can induce polymorphic transformatiosn and it follows that careful quality control is necessary at all stages to monitor undesirable changes.

Taday et al. p. 831 states "Once in the desired crystalline form, the polymorphis state *may be changed* by incorrect storgage or even during tablet preparation and p. 836, figure 8, wherein compound of four form in pharmaceutical composition resulted in similar spectra, *i.e.,* form.

The pharmaceutical composition field has well recognized that stability of an active principle i.e. specific polymorphic form of a compound, has no predictability on its outcome in composition processing. It is known in the art that:

--Singhal et al. "..It should be pointed out that a major portion of any formulation effort is the choice of exipients and processes which minimize the chemical instability of the drug…." P.338, left col.

--CMU phar. Polymorph. "there are a number fo examples in which polymorphic molecules change crystal structure under processing conditions while in contact with liquids or solid material. In these enviroments, it is difficult to apply standard techniques to identify the predict the transformation…." See p.1-2 para.

> --US 6,627,646, col. 1-2, especially, "..from thermodynamic considerations only one polymorph will be stable;.....however, thermodynamic stability is not sufficient to ensure that the stable polymorph will always be produced…….most transformations occur in suspension and are solvent mediated…..other transformations are irreversible over a broad range of temperature:

The amount of guidance/experimentation and working examples

On page 8 of the specification, it was explicitly disclosed that for pharmaceutical composition of the crystalline forms, the carriers are selected from the generally know agents such as "water, vegetable oil, alcohol……." to form into suspension, emulsion, liquid etc. Please note that all liquids are non-crystalline, thus, are known to abolish crystallinity.

The specification provided no description or enablement as to how the newly acquired "form" can be prepared into a composition which can maintain the particular crystalline structure without the conventional recognized conversion to other forms i.e. amorphous form in liquid, emulsion etc. Per ponderous of evidence in the prior art indicated that for a given polymorph, *absent of any description or enablement* from the specification, does not *automatically* keeps its form in the pharmaceutical composition. Therefore, absent of description or enablement in the specification, the mere listing of a general pharmaceutical carriers does not *automatically* keeps its form in the pharmaceutical composition.

It has been delineated by evidence of the field, transformation of polymorph in pharmaceutical composition is not chemical stability of a crystalline form alone but its interaction with material and condition while composition is being made. As clearly evidenced on pages7-9, processing for composition including conventional and liquid material which are well known to abolish crystallinity of a compound. The synthesis, isolation and characterization

of a crystal, thus, provided no description or enablement that how such crystallinity, stability or physical characteristic of the isolated "form" will be incorporated and stayed in a formulation.

Further, the specification has also not described how the crystalline forms in the compositions being claimed will be maintained and prevented from converting to other forms when used in the treatment the inhibition of gastric secretion in the stomach. It is well recognized in the art that the compound is given to the subject in a physiological environment, *i.e.,* administered. As discussed supra, there is no description or enabling support that the instant polymorph will be in its physical form and biological activity results from the particular form instead of the solution state of the compound.

In view of the per ponderous of evidence as delineated supra, it is well recognized in the art that for a given crystalline form of a drug, *in absence of explicit* enabling description, in view of the high degree of unpredictability, even if one is in possession of a particular crystalline form, no predictability can be found that such forms will prevail in pharmaceutical compositions.

Applicants' assertions and allegations in the instant response do not take the place of objective evidence. Applicants have failed to show that polymorph in the composition will maintain its form after pharmaceutical formulation. Applicants have provided no objective evidence that the instant polymorphs will not be identical to the prior art because *"when a crystalline solid is dissolved in solvent, the crystalline structure is lost so that different polymorphs of the same substance will show the same absorption spectra as solution"* (see Jain p.316). Further, in the aqueous phase, *all physical forms are amorphous* (see Ulicky). It is well recognized in the art that for a given crystalline form of a drug, *in absence of explicit* enabling description, in view of the high degree of unpredictability, even if one is in possession of a

particular crystalline form, no predictability can be found in such form will prevail in pharmaceutical compositions. See Chemical & Engineering News.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13-18, 41 and 45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Again, claims 13-18, 41 and 45 contains the generic name pantoprazole. Where a generic name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the generic name cannot be used properly to identify any particular material or product. In the present case, the genreric name is used to identify/describe a chemical compound and, accordingly, the identification/description is indefinite. Again, the name pantoprazole does not properly identify the chemical structure of the compound.

Again, only the chemical IUPAC name identifies the compound having a specific chemical structure.

The claims measure the invention. United Carbon Co. V. Binney & Smith Co., 55 USPQ 381 at 384, col. 1, end of 1st paragraph, Supreme Court of the United States (1942).

The U.S. Court of Claims held to this standard in Lockheed Aircraft Corp. v. United States, 193 USPQ 449, AClaims measure invention and resolution of invention must be based on what is claimed.

The C.C.P.A. in 1978 held that an invention is the subject matter defined by the claims submitted by the applicant. We have consistently held that no applicant should have limitations of the specification read into a claim where no express statement of the limitation is included in the claim. In re Priest, 199 USPQ 11, at 15.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia L. Morris whose telephone number is (571) 272-0688. The examiner can normally be reached on Mondays through Fridays.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR

system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Patricia L. Morris/
Primary Examiner, Art Unit 1625

plm
May 8, 2008